Exhibit B

THE KIDNEY

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It should be noted that patients with heavier proteinuria and more severe disease may show a diminution of protein excretion when recumbent, but by definition, excretion rates will not decrease to less than 150 mg/24 hours.

Microalbuminuria

The excretion of albumin at rates not detectable by routine dipstick urinalysis but clearly above normal levels has been termed microalbuminuria (101,229). As discussed earlier, this rate of excretion has been defined to be between 20 and 200 μg/minute (or 30 to 350 mg/day). Although microalbuminuria can be found in a variety of conditions including hypertension, preeclampsia, syphilis, fever, skin disease, acromegaly, infection, and drug ingestion, the measurement of small quantities of albumin in the urine has been most extensively evaluated in diabetes mellitus (65,97,129,190,249,252,254–256,317,318). When cohorts of type 1 diabetics without dipstick-positive proteinuria were monitored for up to 14 years, increased rates of urinary albumin excretion predicted which patients would develop overt diabetic nephropathy (defined as proteinuria detectable by dipstick methods) (213,231,251,342). The predictive level of albumin excretion in these studies varied from 15 to 70 μg/min, most likely related to different sampling methods and different periods of follow-up. The finding of increased albumin excretion before the onset of overt nephropathy has given rise to the term incipient diabetic nephropathy, a stage defined by the presence of microalbuminuria in two of three urine samples collected consecutively within a 6-month period (72,101,229). Other abnormalities associated with diabetes and that may be associated with incipient nephropathy include glomerular hyperfiltration, systemic hypertension, retinopathy, increased transcapillary escape rate of albumin, and a variety of renal morphologic changes including GBM thickening, mesangial expansion, and the presence of fibrotic glomeruli (101,214,229). In a recent study examining the relation of microalbuminuria to renal structural changes, increased albumin excretion when present with hypertension, decreased creatinine clearance, or both, were associated with established abnormalities of glomerular structure including increased GBM thickness and mesangial expansion (63). This study suggests that microalbuminuria is not simply a predictor of diabetic nephropathy but rather is a marker of early nephropathy. Once present, the rate of protein excretion increases by about 20% per year (66). In type II diabetics, microalbuminuria is a poor predictor of future nephropathy, perhaps related to other causes of albuminuria in these usually older patients (16,98,230). However, increased albumin excretion in non–insulin-dependent diabetics predicts nonrenal mortality, such as coronary artery and other macrovascular disease (165,227,308). As in diabetics, microalbuminuria represents a risk factor in nondiabetic hypertensive populations (358). In a prospective study of middle-aged hypertensive men with microalbuminuria, one third developed cardiovascular disease, many more than in a control group without microalbuminuria (205). Other studies also have shown that microalbuminuria in nondiabetic Mexican Americans was associated with a higher incidence of hypertension, hyperlipidemia, and myocardial infarction (128). Peripheral vascular disease also is known to occur at a higher frequency in those with microalbuminuria (141). Presumably, the albumin leakage through the glomerular capillary is indicative of more systemic toxic effects and/or general susceptibility of the vasculature in certain patient populations.

Tubulointerstitial Disease

The general clinical grouping of chronic renal disease into glomerular and tubulointerstitial varieties is, to a large extent, arbitrary, with considerable overlap when renal structure and function are analyzed carefully. Nevertheless, patients who sustain predominantly toxic injuries to the renal tubular epithelium, such as those with heavy metal poisoning or certain metabolic diseases, may manifest proteinuria due largely to inability to reabsorb normally filtered small–molecular-weight proteins (132,264,266,279). This condition is detectable by qualitative examination of urine by immunoelectrophoresis. Patients with disease that is initially tubulointerstitial in its origin can develop mixed patterns of protein excretion with both glomerular leakage of albumin and large–molecular-weight proteins due to glomerular injury as well as concomitant increased excretion of β_2-microglobulin, lysozyme, and other small–molecular-weight proteins due to dysfunction of the tubular absorptive mechanisms. In general, tubular proteinuria, when relatively pure, results in total protein excretion less than 2 g/24 hours. It can be diagnostically categorized with urine electrophoresis, demonstrating large amounts of several small proteins, or by assaying for any of the specific small proteins normally filtered but normally reabsorbed (105,130).

Glomerular Disease

Clinical Classification

Virtually all chronic glomerular injuries result in proteinuria. Although proteinuria is one of the hallmarks of the nephritic syndrome, this discussion primarily focuses on the nephrotic syndrome. The nephrotic syndrome is defined by the constellation of high rates of proteinuria (>3.5 g/24 h), hypoalbuminemia, edema, and hyperlipidemia. Although all of these features are present in patients diagnosed as nephrotic, their degree of expression may vary considerably. A large number of primary and secondary diseases are clinically expressed as the nephrotic syndrome (152,240). The major types and approximate incidence of primary glomerular diseases resulting in adult nephrotic syndrome are listed in Table 82-2.

TABLE 82-2. CAUSES OF IDIOPATHIC NEPHROTIC SYNDROME IN ADULTS

Disease	Incidence (%)
Membranous	40
Minimal-change disease	20
Focal glomerular sclerosis	20
Membranoproliferative	10
Other	10